REMARKS

Claims 1 to 24 are pending. Claims 1 and 7-9 are currently amended. Claim 25 stands withdrawn from consideration.

Claim 1 is currently amended to clarify that the "at least one model compound" differs from the "at least one pharmaceutical compound." It is submitted that this feature is implicit and supported throughout the specification and claims; for example, see the specification on page 1, lines 14-19; on page 2, lines 5-7; on page 6, lines 22-24; and on page 11, lines 7-10.

Further, it is submitted that the very word "model" indicates that the model is a comparison material for the pharmaceutical. For example, "The Random House Dictionary of the English Language" Second Edition, Unabridged, S.B. Flexner, Ed.: Random House, New York, ©1987, pages 1235-1236 (enclosed as Attachment A) defines the word "model" in pertinent part as:

"1. a standard or example for imitation or comparison ..."

Claims 7-9 are currently amended to clarify the antecedent basis of the claims. Support for the amendments may be found in the specification on page 8, lines 15-24 and in original claims 1, 6 and 7-9.

§ 103 Rejections

Claims 1-5, 8, and 10-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al [Journal of Pharmaceutical Sciences, 1965, volume 54, pages 591-594] in view of Loftsson et al. [Drug Development and Industrial Pharmacy, 1994, volume 20, pages 1699-1708] in view of Tayar et al. [Journal of Pharmaceutical Science, volume 80, 1991, pages 590-598].

The Patent Office submits that Katz et al. list molecular weights and partition coefficients for a plurality of molecules. The Patent Office argues that molecular weights are deduced from the columns in Table 1 (Katz et al. page 593) listing the combination of weight by volume concentrations and the molar concentrations. The Patent Office further submits partition coefficients are listed in the fifth column of data. The Patent Office submits that the McKenzie

parameter (p McK-S_{50}) is calculated in the last column as the negative logarithm of dilution producing vasoconstriction of 50% of subjects while the partition coefficients are experimentally measured. The Patent Office further submits that Katz et al. disclose the requirement of skin of a live mammal, and that the entire system comprises a transdermal delivery system.

The Patent Office concedes that Katz et al. fail to teach the compound-excipient formulation, the diffusion method and analysis, saturation of the model compound, impact of rotatable and hydrogen bond donors and acceptors, use of a Franz cell(s), a plurality of excipients, utilization of a chemical reaction, use of a synthetic polymer membrane, calculated and empirical parameters of the pharmaceutical, and a transdermal delivery system. The Patent Office further concedes that Katz et al. fail to teach a partition coefficient between octanol and water (log (P)).

The Patent Office submits that Tayar et al. teach the solvation of solutes in different solvent systems (including octanol-water) to tune for a desired comparison of aqueous solvability to lipophilicities.

The Patent Office further submits that Loftsson et al. teach a method of making a pharmaceutical composition between hydrocortisone and different cyclodextrins to enhance transdermal delivery, and that Loftsson et al. teach a relationship between diffusion through a membrane and cortisone concentration as the combination of the hydrocortisone and each of the cyclodextrins used in the formulation.

The Patent Office further submits that Loftsson et al. teach an excess of cyclodextrin concentration used to saturate the hydrocortisone.

The Patent Office further submits that Loftsson et al. disclose that the type of molar substitution chosen for the cyclodextrin affects its size, number of rotatable bonds, and hydrogen bonding characteristics. The Patent Office further submits that Loftsson et al. disclose that Franz diffusion cells are used to measure diffusion across hairless mouse skin. The Patent Office further submits that Loftsson et al. disclose that the chemical reaction between the cyclodextrin and the hydrocortisone is used to affect the diffusion across the skin. The Patent Office further submits that Loftsson et al. disclose that the formulation is chosen from one of two different cyclodextrins employed throughout the study. The Patent Office further submits that Loftsson et

al. disclose (in Table 2) that the standard deviation of the flux needs to be calculated while the flux is an experimentally measured property.

The Patent Office argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine the general corticosteroid study of Katz et al. with the cyclodextrin study of Loftsson et al. and the partition study of Tayar et al. because both Katz and Loftsson investigate cortisones as drugs with the added advantage of Loftsson having the feature of cyclodextrins to enhance drug performance, and since Tayar et al. is a variation on the type of partition coefficient measured in Katz et al. The Patent Office further argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to adjust the partition study of Katz et al. from water-ether to water-octanol according to the procedures of this study of Tayar et al. for a desired comparison of aqueous solvability with lipophilicities.

Claim 1 is currently amended to address the Examiner's analysis, found in the Response to Arguments section of the present Office Action, that the pharmaceutical may serve as its own model compound. Accordingly, it is submitted that such an analysis no longer applies.

In view of the foregoing, and notwithstanding the Patent Office's characterization of Katz et al., Tayar et al., and Loftsson et al., which Applicants do not concede, it is submitted that one of ordinary skill in the art at the time the invention was made would not be properly motivated to combine the references, as applied by the Patent Office, to achieve the invention of claim 1, and that the such combination is the result of impermissible hindsight reasoning. For example, while Loftsson et al. may use hydrocortisone as a sample drug in their study of HPβCD/drug concentration effects (see Loftsson et al. on page 1700 last sentence, and Abstract), it is submitted that Loftsson et al do not teach or properly suggest that the drug was selected based on a comparison of parameters of a different pharmaceutical, much less parameters consisting of at least log(P) and molecular weight as in currently amended claim 1.

Further in this regard, it is submitted that Katz et al. fail to teach or suggest at least the octanol/water partition coefficient log(P) (e.g., see the specification on page 4, lines 6-8). For example, the partition coefficient PC of Katz et al. is determined using ether-water not octanol-water. In addition, it is submitted that to any extent that Katz et al. may rely of parameters

dependent in part on molecular weight, it is wholly unclear that one of ordinary skill would be properly motivated to select molecular weight *per se* as a criterion (e.g., as required by currently amended claim 1) for use in a method according to currently amended claim 1.

Still further, while Katz et al., Tayar et al., and Loftsson et al. may individually relate to studies of factors relating to membrane diffusion, and in the case of Loftsson et al. selection of appropriate excipients for given pharmaceuticals, it is submitted that they do not, whether taken alone or in combination, teach or properly suggest at least "comparing parameters of at least one pharmaceutical and a plurality of compounds, wherein the parameters consist of at least log(P) and molecular weight" much less "choosing at least one model compound based on the compared parameters from the plurality of compounds for each pharmaceutical, wherein the at least one model compound is different from the at least one pharmaceutical" or further "providing at least one model compound-excipient formulation comprising at least one model compound and at least one excipient; measuring the diffusion of a model compound of at least one model compound-excipient formulation across at least one membrane; choosing a model compound-excipient formulation based on the measured model compound diffusion; and combining components comprising the at least one pharmaceutical and the excipient package of the chosen model compound-excipient formulation" as in currently amended claim 1.

With regard to claims 3 and 4, it is submitted that the parameters: a) number of freely rotatable bonds and b) number of hydrogen bond donors and acceptors, refer to the parameters of the at least one pharmaceutical and the at least one model compound - not the excipient (i.e., cyclodextrin). As such it is submitted that the combination of Katz et al. in view of Tayar et al. in further view of Loftsson et al. fails to teach or properly suggest at least these features.

With regard to claim 15, as discussed above, the combination of Katz et al. in view of Tayar et al. in further view of Loftsson et al. fails to teach or properly suggest that the parameters consist of log P and molecular weight.

For at least these reasons, it is submitted that currently amended claim 1, and hence dependent claims 2-5, 8, and 10-24 are patentable. In summary, the rejection of claims over the combination of claims 1-5, 8, and 10-24 under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. has been overcome and should be withdrawn.

Claims 1 and 6-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al. [Chemistry- A European Journal, 1999, volume 5, pp. 897-901].

The Patent Office submits that Katz et al., Loftsson et al., and Tayar et al. disclose the drug formulation process as stated in the instant application, but concedes that they fail to disclose any use of fluorescence or fluorescence spectroscopy. The Patent Office further submits that Garcia-Ochoa et al. disclose the use of fluorescence and fluorescent spectroscopy to detect the cyclodextrins.

The Patent Office argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz et al. in view of Loftsson et al., in view of Tayar et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al., since Garcia-Ochoa et al. is an extension of the cyclodextrin study with the use of fluorescence to more effective monitor cyclodextrin concentration and location.

In response, Applicants submit that currently amended claim 1 is patentable over the combination of Katz et al. in view of Loftsson et al. in view of Tayar et al. for at least the reasons discussed hereinabove. It is submitted that Garcia-Ochoa et al., which concerns a study of the fluorescence of molecules within the environment of a cyclodextrin cavity, fails to supply the deficiencies of Katz et al. in view of Loftsson et al. in view of Tayar et al. Regarding claim 7, applicants note that fluorescence spectroscopy is used to measure the diffusion of at least one model compound across at least one membrane.

In summary, the rejection of claims 1 and 6-7 under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa et al. has been overcome and should be withdrawn.

Claims 1 and 8-9 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Katz et al. in view of Loftsson et al., in view of Tayar et al., in view of Garcia-Ochoa et al.

as applied to claims 1 and 6-7 above, and further in view of Colarusso et al [Biophysical Journal; February 2002; volume 82, pages 752-761].

The Patent Office submits that Katz et al., Loftsson et al., Tayar et al., and Garcia-Ochoa et al. teach of method of formulating a drug using a cortisone and a cyclodextrin and fluorescence, but concedes that they fail to record any images in their studies. The Patent Office submits that Colarusso et al. illustrates several fluorescent images of cells and the effects of cyclodextrins on them.

The Patent office argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz et al. in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa et al. as applied to claims 1 and 6-7 above, and further in view of Colarusso et al. since Colarusso et al. use cyclodextrins in analyzing images of cells.

In response, Applicants submit that currently amended claim 1 is patentable over the combination of Katz et al. in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa for at least the reasons discussed hereinabove. It is further submitted that Colarusso et al., which concerns fluorescence of stained cells of a membrane (e.g., see Colarusso et al. in the abstract) fails to supply the deficiencies of Katz et al. in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa et al. Regarding claim 7, Applicants submit that the fluorescence spectroscopy is used to measure diffusion across at least one membrane, not study stained biological cells as in Colarusso et al.

In summary, the rejection of claims 1 and 6-7 under 35 U.S.C. § 103(a) as being unpatentable over Katz in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Colarusso et al. has been overcome and should be withdrawn.

Rejoinder

In view of the foregoing discussion, rejoinder and allowance of withdrawn claim 25 is respectfully requested.

Conclusion

In view of the above, it is submitted that the application is in condition for allowance. Reconsideration of the application is requested.

The Examiner is invited to contact the undersigned to discuss any matters that may be readily resolved by a telephonic conversation.

Respectfully submitted,

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